UNIVERSITY OF GONDAR
COLLEGE OF MEDICINE AND HEALTH SCIENCES
INSTITUTE OF PUBLIC HEALTH

Body mass index variation over time and associated factors among HIV infected adult patients on second line ART in Amhara region, Ethiopia

A THESIS REPORT SUBMITTED TO THE INSTITUTE OF PUBLIC HEALTH, COLLEGE OF MEDICINE AND HEATLH SCIENCES, UNIVERSITY OF GONDAR IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PUBLIC HEALTH IN EPIDEMIOLOGY AND BIOSTATISTICS.

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BMI variation over time and associated factors among HIV infected adult patients on second line ART in Amhara region, Ethiopia 2017

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ACRONYUM/ABREVATIONS

ABC	Abacavir
AIC	Akaike's Information Criterion
AIDS	Acquired Immuno Deficiency Virus
ART	Anti-Retroviral Therapy
BIC	Bayesian information criterion
BMI	Body Mass Index
CI	Confidence Interval
CPT	Co-trimoxazole preventive therapy
FMOH	Federal Ministry Of Health
HAART	Highly Active Anti-Retroviral Therapy
HIV	Human Immuno Deficiency Virus
Kg	Kilogram
NGO	Non Governmental Organizations
OIs	Opportunistic Infections
PLWHA	People Living With HIV/AIDS
TB	Tuberculosis
TDF	Tenofovir
UNAIDS	United Nations programme on HIV/AIDS
WHO	World Health Organization
ZDV/AZT	Zidovudine

Abstract

Introduction: In Ethiopia human immunodeficiency virus adult prevalence is estimated to be 1.14% in 2014. In the same year there were an estimated 0.8 million people living with HIV and there were also approximately 35,600 AIDS related deaths in the country. There are more than 300,000 people who are on ART among which 1.5% are on second line in the country. Body weight of HIV patients has been an important diagnostic and evaluation measure. It is recognized as one of the first criteria for the clinical definition of acquired immuno deficiency syndrome. It is also an important predictors of treatment outcome, dropout rate from HIV care, and risk of death. But there is lack of information how it is changing over time and the predictors affecting it in HIV patients already on ART.

Objective: The objective of this study was to assess the trend of BMI over time and factors affecting it among HIV patients on second line ART in Amhara region.

Methods: Institution based retrospective follow up study was conducted among adults on second line ART in referral hospitals Amhara region. Total 1016 patients were included in the study. Data were collected from patient charts and entered to EPI info version 7 and was analyzed using STATA version 14.0. Summary measures were done for baseline characteristics. Exploratory data analysis for the body mass index of patients including individual profile plot, mean profile plot was done. Predictors with p value < 0.25 in bivariable analysis were entered to the final linear mixed model.

Result From a total of 1016 participants 538 (52.95%) were males and median age of participants was 33 (IQR=14). Median follow up time was 17 months. The evolution of BMI showed variation between individuals and within individuals over time. The average change of BMI has showed a positive linear increase over time. Significant predictors of BMI were treatment duration (β=0.04 95% CI 0.01, 0.07), age (β=0.04 95% CI 0.01, 0.07), NGO employement (β =1.9 95% CI 0.24, 3.52) good adherence **(**β=0.6 95% CI 0.04 1.14**)** INH prophylaxis (β =0.7, 95% CI 0.22, 1.36), CPT (β=0.8, 95% CI 0.25, 1.39), ambulatory (β=1.6, 95% CI -1.91 -1.26), bedridden (β=1.8, 95% CI -2.45 -1.21), WHO stage III (β = -0.4 95% CI -0.62 -0.16), WHO stage IV (β=-0.8 95% -1.17 -0.36) and CD4 count (β =0.001 95% CI 0.0007, 0.0014). Time interaction of tertiary education (β=0.02, 0.003, 0.04), ambulatory (β =0.03 95% CI 0.013 0.05), WHO stage III (β =0.01 95% CI 0.013 0.02).

Conclusion and recommendations There was a linear increment of BMI over time in HIV patients on second line ART. Age, treatment duration, INH prophylaxis, CPT prophylaxis, Occupational status, CD4 count, ART adherence, Functional status, WHO stage were significant predictors of BMI. Prophylaxis for opportunistic infection shall be given to all patients, good adherence, staying long on treatment shall be enhanced.
KEY WORDS Amhara, BMI, HIV, Second line ART, Linear mixed effect model

1. INTRODUCTION

1.1 STATEMENT OF THE PROBLEM

Human immunodeficiency virus/Acquired Immunodeficiency syndrome (HIV/AIDS) is one of the most destructive diseases human kind has ever faced. In 2015 there were 2.1 million [1.8 million–2.4 million] new HIV infections worldwide, adding up to a total of 36.7 million [34.0 million–39.8 million] people living with HIV. The disease is a leading cause of death worldwide. Since the beginning of the pandemic, more than three decades ago; approximately 30 million people have died of AIDS-related illnesses(1, 2).

From the world total population of people living with HIV, 71% are found in sub-Saharan Africa. Ten countries including Ethiopia account for 81% of all people living with HIV in the region and the estimated AIDS related deaths were 1.1 million in 2013(3).

In Ethiopia HIV adult prevalence is estimated to be 1.14% in 2014. In the same year there were an estimated 769,600 people living with HIV and there were also approximately 35,600 AIDS related deaths in the country(4).

The introduction of anti retroviral therapy (ART) has resulted in a massive reduction in the mortality of HIV patients(5). In 2014 globally as many as 13,950,296 people were accessing ART(3). In 2013/14 in Ethiopia 308,860 to 344,344 people living with HIV/AIDS (PLWHA) were using ART. Among which 1.5% were on second-line treatment. The Amhara regional state in northwest Ethiopia comprises the highest proportion of ART users, with 102,088 individuals(6).

Body weight of HIV patients has been an important diagnostic and evaluation measure. It is recognised as one of the first criteria for the clinical definition of AIDS. The current World Health Organization (WHO) clinical staging of the disease also includes moderate unexplained weight loss (<10% presumed or measured body weight, stage 2), unexplained severe weight loss (>10% of body weight or BMI $\leq$ 18.5 kg/m^2, clinical stage 3) and HIV wasting syndrome (Unexplained severe wasting, stunting or severe malnutrition, clinical stage 4) as criteria to define advanced HIV infection(7).

Weight loss and wasting remain common problems and also the strongest independent predictors of mortality even in the era of highly active antiretroviral therapy (8, 9).

Increment in BMI of patients is generally associated with a better CD4+ T cell recovery(10). The risk of death from AIDS is also higher in patients who are underweight when compared to those who are normal and overweight/obese(11). In the era of effective ART being overweight and obese has also become another growing problem exposing HIV patients to several chronic illnesses in addition to the virus itself. (12)

The BMI of HIV patients is affected by different factors including gender, age at ART initiation, baseline CD4 count, initial body weight, initial hemoglobin, (13) viral load, CD4 count change(14) presence of Tuberculosis and other opportunistic infections, adherence to treatment and marital status(15)

Even though there is a high early mortality in patients on second line ART (16) most of the literatures conducted on this key factor which determine mortality, are done in patients on first line ART and are also conducted in developed countries. This study will answer the research question that how the BMI of patients on the second line ART is changing and what factors are affecting it. The findings of this study will be a good input for all decision or policy makers at every stage of the health care system to reduce mortality due to the disease.

1.2 LITERATURE REVIEW

1.2.1 Trend of Body Mass Index

BMI of HIV patients is among the many important staging criteria and an important prognostic factor determining the outcome of the disease. Studies show that the mortality and morbidity of these patients is highly affected by the change in their BMI. Especially before the initiation of HAART weight loss and wasting have been major co-morbidities. And this problem has continued even in the era of HAART (7-9). On the other hand there is also an emerging and fast growing problem related to ART that is excessive weight gain leading to a high occurrence of overweight and obesity in HIV patients.(12) a study showed that for a one unit increase in BMI of HIV patients the risk of cardio-vascular events have increased by 18%-20%(17).

Treatment outcome of patients was found to be significantly associated with their body weight change (18-21). A study conducted in sub-Saharan Africa showed weight loss of $\geq$ 10% as an important predictor of dropout from care after ART is initiated (22).

The risk of death for these patients is also associated with their body weight (16, 23-26). In a study conducted in South Africa the prevalence of overweight has increased by 10% from 27% baseline to 37% after one year of antiretroviral therapy. Whereas underweight prevalence has decreased by 5% from the baseline.(27)

HIV patients can get or loss weight depending on many factors. In a study conducted in Abidjan the prevalence of being overweight or obese increased significantly among women, from 30 % at baseline to 38 % after two years of follow up, but remained unchanged among men(28). Another follow up study found the prevalence of wasting in patients on ART to be 14%. Significantly large proportion of this cohort (58%) continues to lose weight and 33% met one of the definitions of HIV-associated wasting (9).

In a systematic review conducted on association between nutritional status and the immune response in HIV positive patients under HAART, weight loss is still prevalent among these patients in Low and Middle Income Countries and contribute to excess early mortality(29).

1.2.2 Factors affecting body mass index

Studies have been conducted to determine factors affecting the weight change in HIV patients on ART. In a study conducted in resource limited settings from the Southern-, East-, West- and Central African regions and the Asia-Pacific region weight change in the first year after initiation of ART is higher in men than women, men loss weight when women stay the same, and after second year of therapy women are more likely to have weight gain as compared to men (13). A study conducted in Tanzania showed that women have decreased risk of significant weight loss after ART initiation when compared to men. The same study also showed that age to be significant predictor of weight change, with older patients having higher risk of long term weight loss(30). Another study conducted in Cameroon also showed that age group of less than 30 years and married individuals had a good evolution(15). But a study in low resource setting found patients younger than 29 years old to have a higher risk of weight loss as compared to those with in the age group of 35 to 40 years(13).

A study conducted in Hanoi, Vietnam showed moderate/high alcohol drinking, tobacco smoking, and poor adherence are significantly associated with negative weight change(31).

In a study conducted in Tanzania as the hemoglobin level of patients increases the risk of significant weight loss has decreased.CD4 count increment of HIV patients is also inversely related with risk of weight loss (30). Baseline CD4 count $\leq$ 200 was found to be significantly associated with negative change in weight, and CD4 Count greater than 199 at baseline was significantly associated with lower risk of weight loss $\geq$ 5% in studies conducted in Hanoi, Vietnam and resource limited settings respectively(13, 31). An increase in the viral load of patients is associated with a negative change in the body weight. Weight change also has a significant difference with respect to duration of treatment (14, 15, 31). But, in a study conducted in South Africa, neither ART duration & CD4 count nor viral load was independently associated with body weight change(32). Body weight change of patients is also determined by baseline WHO stage. The higher the WHO stage the higher risk of weight gain. Patients with lower baseline weight have also positive change in their weight than those with higher baseline weight (13). The presence of Opportunistic infections was significantly associated with negative change (15). Whereas presence of Tuberculosis had no effect on weight change(33).

Treatment Related Factors

Antiretroviral therapy regimen and duration of therapy are also significant predictors of the body weight change (13, 20, 34).

1.2.3 CONCEPTUAL FRAMEWORK

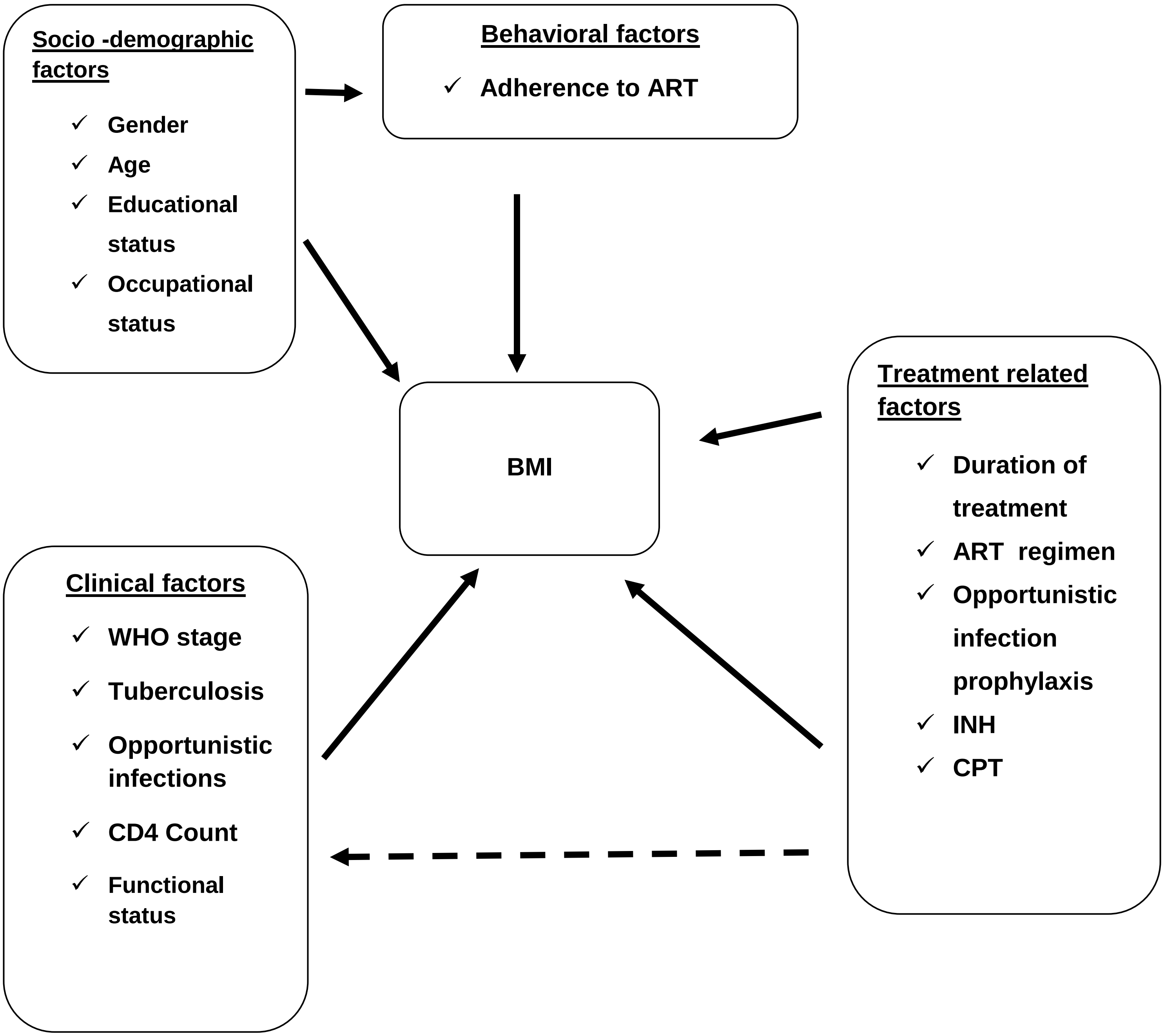


Figure 1 Conceptual Framework adopted from review of literatures (14, 16, 21, 32, 34).

1.3 JUSTIFICATION OF THE STUDY

Although the BMI of HIV infected patients is an important predictor of mortality and other treatment outcomes, there is lack of information on this important predictor especially in our country. Most of published studies conducted are on patients in developed countries. And even those few studies conducted in similar settings have used models that don't show the change over time. Since this study is conducted using repeated measure (linear mixed effect model) which can show the changes over time, includes both time varying and non time varying predictors, and random effects, it will fill both the lack of information and methodological gaps. We believe the results of the study can help decision making, program evaluation and help to identify the possible intervention areas to decrease morbidity and death from the disease.

The results of this study will also be a good input for future researches.

2. OBJECTIVES

2.1 General Objective

- ✓ To examine trend of BMI over time and factors affecting it among adult HIV infected patients on second line ART in Amhara region, from February 2008 to February 2016

2.2 Specific Objectives

- ✓ To examine the trend of BMI over time among adult HIV infected patients on second line ART

- ✓ To determine factors affecting BMI evolution among adult HIV infected patients on second line ART

3. METHODS AND MATERIALS

3.1.0 Study design

Institution based retrospective follow up study was conducted among adults on second line ART

3.1.1 Study area and period

This study was conducted in Amhara regional state which is one of the nine regions of Ethiopia. It has 17 Hospitals, 520 Health Centers and 2,941 Health Posts according to FMOH health and health related indicators report of 2010. There are 102 088 individuals on ART in the region. Referal hospitals in which the study was conducted were Gondar university, FelegeHiwot, Debremarkos, Debrebirhan, Dessee, Finoteselam, Woldya and Debre Tabor Hospitals. These hospitals provide service for the largest proportion of patients on second line ART.

3.1.2 Source population and study population

The source population of this study was all Adults above the age of 24 years who were on second line ART in the Amhara region.

The study population was adult HIV infected patients on second line ART in the selected hospitals who started second line therapy between February 2008 and February 2016.

3.1.3 Inclusion and exclusion criteria

All adults above the age of 24 years who were on second line ART in the selected hospitals were included, however patients whose weight was measured only once, Patients for whom baseline height was not measured and patients who were pregnant were excluded from the study.

3.1.4 Sample size and sampling procedure

We have selected referral hospitals in the region.

The sample size for this study was done based on the following assumption

All subjects measured at m = 10 time points

We used 90% power to detect a difference, d of 0.75 kg/m^2

The sample size formula was taken from sample size for longitudinal studies(35).

$$n = \frac{2\sigma^2(1+(m-1)\rho)(Z\alpha_{/2} + Z_{1-\beta})}{md^2}$$

The standard deviation for calculating the sample size in this study was taken from a study in Kano, Northwestern Nigeria(36).

$$n = \frac{2x6^2(1+(10-1)0.5)(1.96+1.64)}{10(0.75)^2} = 912.38 \approx \underline{\underline{913}}$$

- δ (standard deviation)= 6
- ρ = 0.5 Constant within-subject correlation
- Where α = significant level (0.05)
- 1-β = the power of the study = 90%
- Z1-α/2 =Z-value attributed to α/2 (1.96)
- Z1-β = Z-value attributed to 1-β (1.64)

Sampling Procedure

We have found 1016 patients who fulfill the criteria and have included them in the study

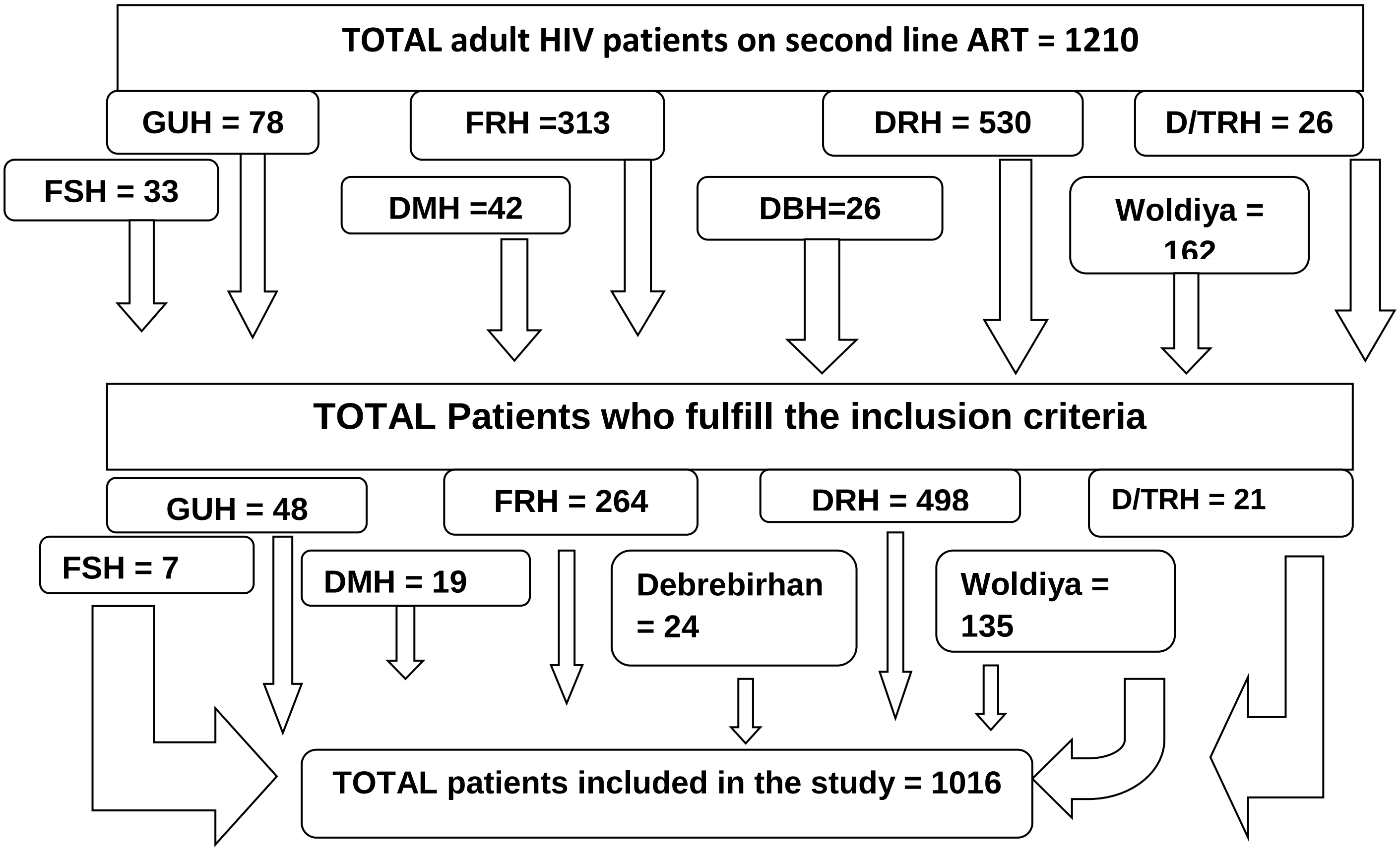


Figure 2 Schematic presentation of the study participant selection

*GUH=Gondar University Hospital *D/TRH= Debretabor Hospital
*FRH = Felegehiwot Referal Hospital *FSH= Finoteselam Hospital
*DRH = Dessie Referral Hospital *DMH= Debremarkos Hospital
*Debrebirhan= Debrebirhan Hospital *Woldiya= Woldiya Hospital

3.1.5 Variables of the study

Dependent variable: Body Mass Index

Independent variables

Socio-demographic variables: Gender, Age, Educational Status, Occupational status

Behavioral Factors**:** Adherence

Treatment Related factors: Duration of Treatment, Isoniazide prophylaxis (INH), Cotrimoxazole Prophylaxis therapy (CPT), ART Regimen.

Clinical Factors: WHO Stage, Tuberculosis, Opportunistic Infections, CD4 count, Functional status

3.1.6 Operational definition

Adherence to ART: Good adherence is when a patient arrives $\geq$ 95% of his or her visits within 3 days or appointment date. Fair adherence is when a patient arrives 85% - 94% of his or her visits within 3 days or appointment date. Poor adherence is when a patient arrives < 85% of his or her visits within 3 days or appointment date.

3.1.7 Data collection tool and Data collection procedures

Data collection tool were prepared in English. Supervised by three health professionals with BSc. degree, twelve health care professionals (Nurses & Public Health Officers) have collected the data after they identified records which meet the inclusion and exclusion criteria.

The quality of data was assured by giving training for data collectors, by close supervision and giving prompt feedback. The collected data was checked for inconsistencies, coding error, out of range, completeness, accuracy, clarity, missing values and appropriate corrections was made by the principal investigator and supervisors.

3.1.8 Data processing and analysis

The data was cleansed & entered in to EPI info version 7 and analyzed using STATA version 14.0. BMI of patients was computed by dividing their weight in kg by baseline hight in meters square. Exploratory data analysis for the weight of patients including individual profile plot, mean profile plot, descriptive and summary statistics were done. Normality assumption was checked by Q-Q plot. To determine the factors associated with BMI of patients univariate analysis for each independent variable was assessed and those found to be significant (p-value<0.25) were selected for the multivariate analysis. The need for random intercept and random slope was checked by likelihood ratio test and finally linear mixed effect model was fitted to evaluate the longitudinal change in the BMI of these patients over time and associations with covariates across all visits. The goodness of fit of the model was checked using a model diagnostic plot.

4. Ethical consideration

Ethical clearance was obtained from Institutional Review Board of Institute of Public Health, CMHS, and University of Gondar. Permission letter was obtained from the hospitals administration and the ART focal persons in all the hospitals. Names and unique ART numbers of patients was not included during data collection.

5. RESULTS

We had a total of 1016 adult patients from which majority of them were taken from Dessie referal hospital 498 (49%). There were a maximum of 12 and a minimum of 2 measurements of weight and other time varying predictor variables. Almost all visits were not balanced in their time of measurements.

5.1 BASELINE SOCIO-DEMOGRAPHIC CHARACTERSTICS

Among the total sample 538 (52.95%) were males. All participants were above or equal to the age of 24 with median age of 33 year (IQR of 14). The largest proportion of these patients 370 (37.11%) were unemployed and 371 (36.9%) have attended secondary school (Table 1).

5.2 CLINICAL AND TREATMENT RELATED BASELINE CHARACTERSTICS

At the initiation of second line ART majority of them 393 (45.54%) were at WHO stage I and 324 (37.54%) were at WHO stage III. Large proportion of participants 871 (86%) were working at base line the rest 114 (11.25%) and 28 (2.75%) were ambulatory and bed ridden respectively. The median CD4 count was 253 with IQR of 252. Regarding the opportunistic infection 661 (66.1%) of the participants had history of at least one opportunistic infection during the follow up time. And 194 (19.38%) patients had history of Tuberculosis. The widely used second line regimen 442 (43.5%) at the initiation was TDF based regimen. INH and CPT was given for 247 (24.87%) and 256 (25.65%) of participants respectively (Table 2, Figure 1).

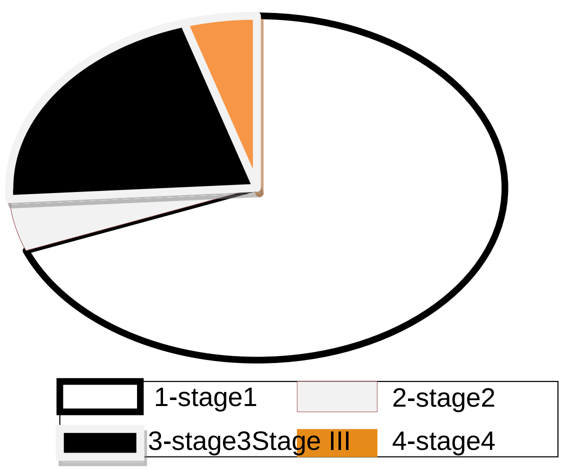


Figure 3 Pie chart of Baseline WHO stage of HIV patients on second line ART in Amhara region 2008 - 2016

Table 1 **Baseline socio demographic characterstics of adult patients on second line ART in Amhara region, 2008 to 2016**

Variables	Number	Percentage
Age		
25-34	547	53.89
35-44	333	32.81
45-54	104	10.25
55-64	26	2.56
$\geq$ 65	5	0.49
Name of Hospital		
Dessie Referal	498	49
Felegehiwot	264	26
Woldie	135	13.3
Gondar University[1]	119	11.7
Sex		
Female	478	47.05
Male	538	52.95
Educational status		
Illiterates	315	31
Primary education	201	19.78
Secondary education	371	31.20
Tertiary education	118	11.61
Occupation		
Unemployed	370	36.41
Governmental	286	28.14
Non-Governmental	21	2.06
Private	66	6.49
Other	254	25

Gondar university[1] :Gondar Universi,Finoteselam,Debremarkos,Debrebirhan,Debretabor

Occupation Others : Daily labourer, students

Table 2 Clinial and treatment related baseline characterstics of adult patients on second line ART in Amhara region, 2008 to 2016

Variables	Frequency	Percentage
WHO Stage		
Stage I	393	45.54
Stage II	66	7.65
Stage III	324	37.54
Stage IV	80	9.27
Functional status		
Working	871	86
Ambulatory	114	11.25
Bed ridden	28	2.75
Opportunistic infection		
No	339	33.9
Yes	661	66.1
Tuberculosis		
No	807	8.62
Yes	194	19.38
CPT given		
No	742	74.36
Yes	256	25.56
INH given		
No	746	75.13
Yes	247	24.87
ART regimen		
ABC based regimen	319	41.4
TDF based regimen	442	43.5
AZT based regimen	197	19.39
Others	58	5.71

Others= entecavir, stavudine based regimens

5.3 BMI status of patients across different visits

At base line 392 (38.5%) of all patients were under weight and 92 (9%) were over weight. As time goes on the under weight status of patients decreases up to the nineth observation and increases to the twelveth observation but the prevalence of overweight increases through out the observations (Figure 4)

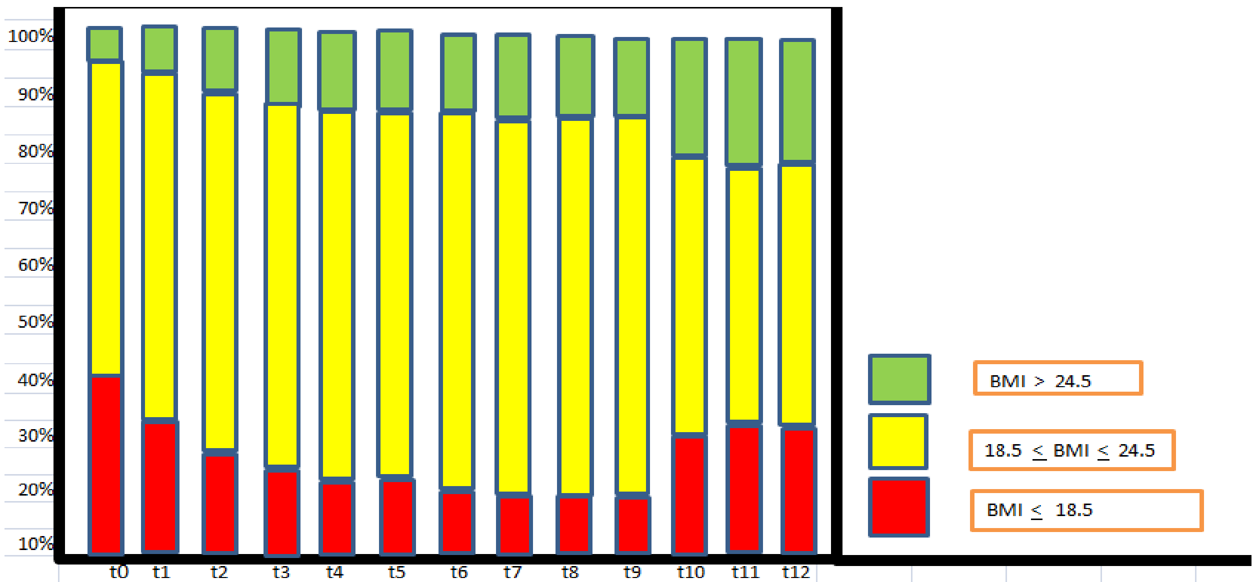


Figure 4 BMI status of patients on second line ART in Amahara region across subsequent visits 2008 to 2016

5.4 EXPLORATORY DATA ANALYSIS

5.4.1 Individual Profile

Before proceeding to the formal statistical analysis we have described the data by exploring how individuals change in BMI over time. To make the individual profile plot more informative we have prepared it for the first 100 individuals (figure 3)

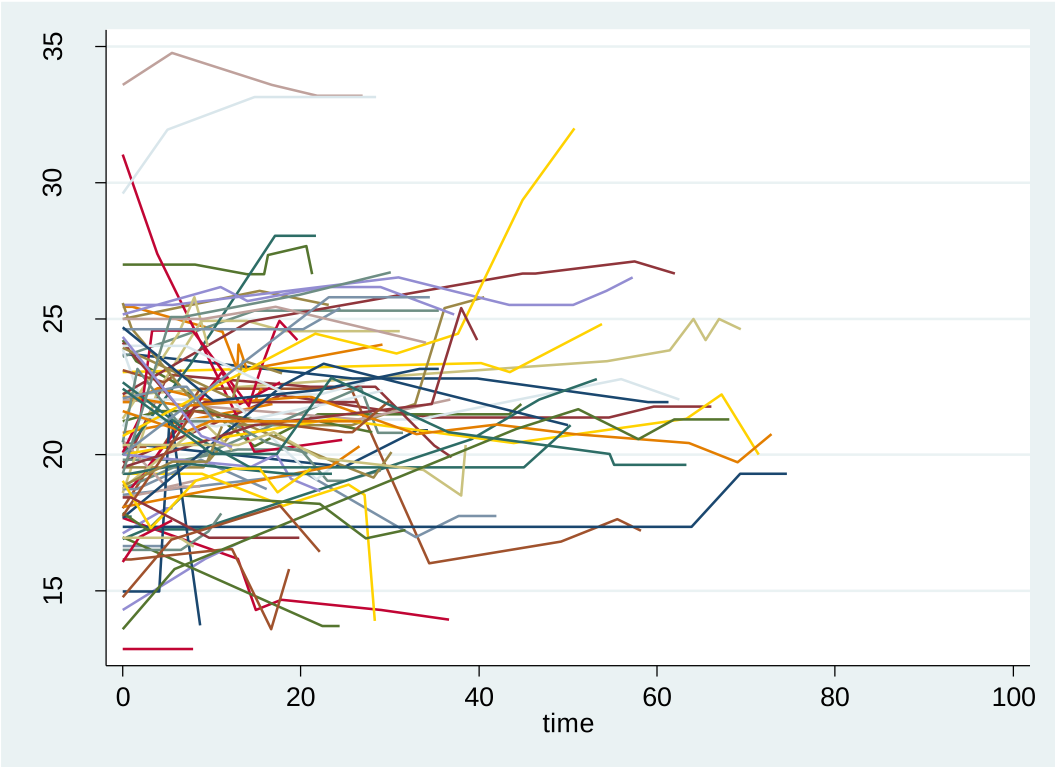


Figure 5 Individual profile plot of BMI over time for the first 100 individuals at second line ART in Amhara region, 2008-2016

According to this plot the BMI status of patients has high variability within an individual over time and variability between individuals at baseline and through time.

5.4.2 Individual profile by sex

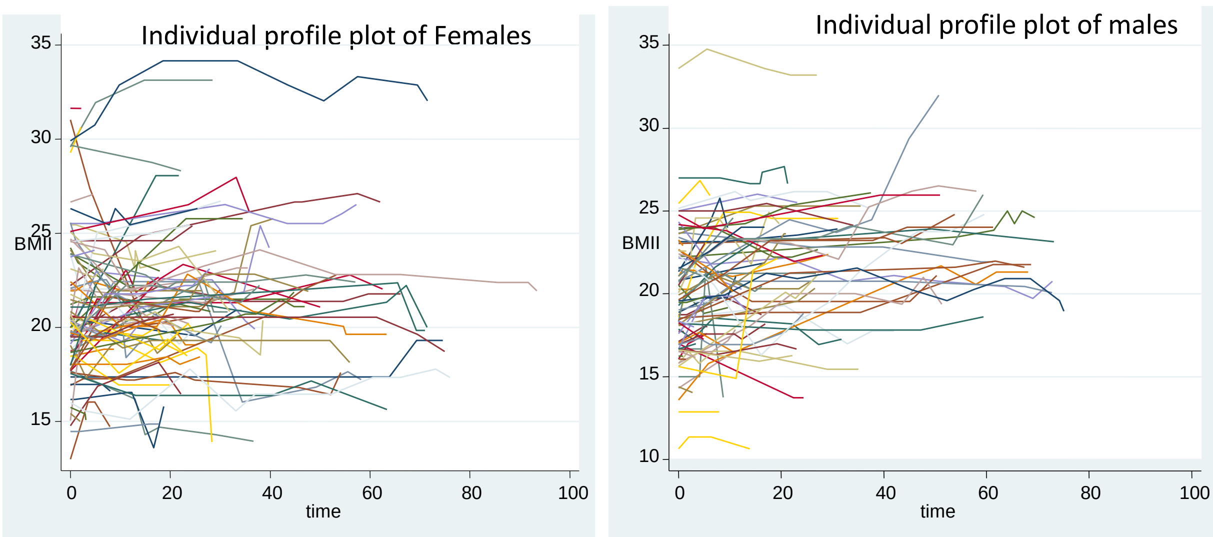


Figure 6 Individual profile for female and male patients on second line ART in Amhara region 2008-2016

There is variation between individuals and within individuals in both male and females.

5.4.3 Exploring the mean profile

Since first objective of the study was exploring the mean of BMI over time. We have used mean profile plot over time. As stated above all measurements in the data have no similar time of measurements therefore we have used smoothing to determine its evolution.

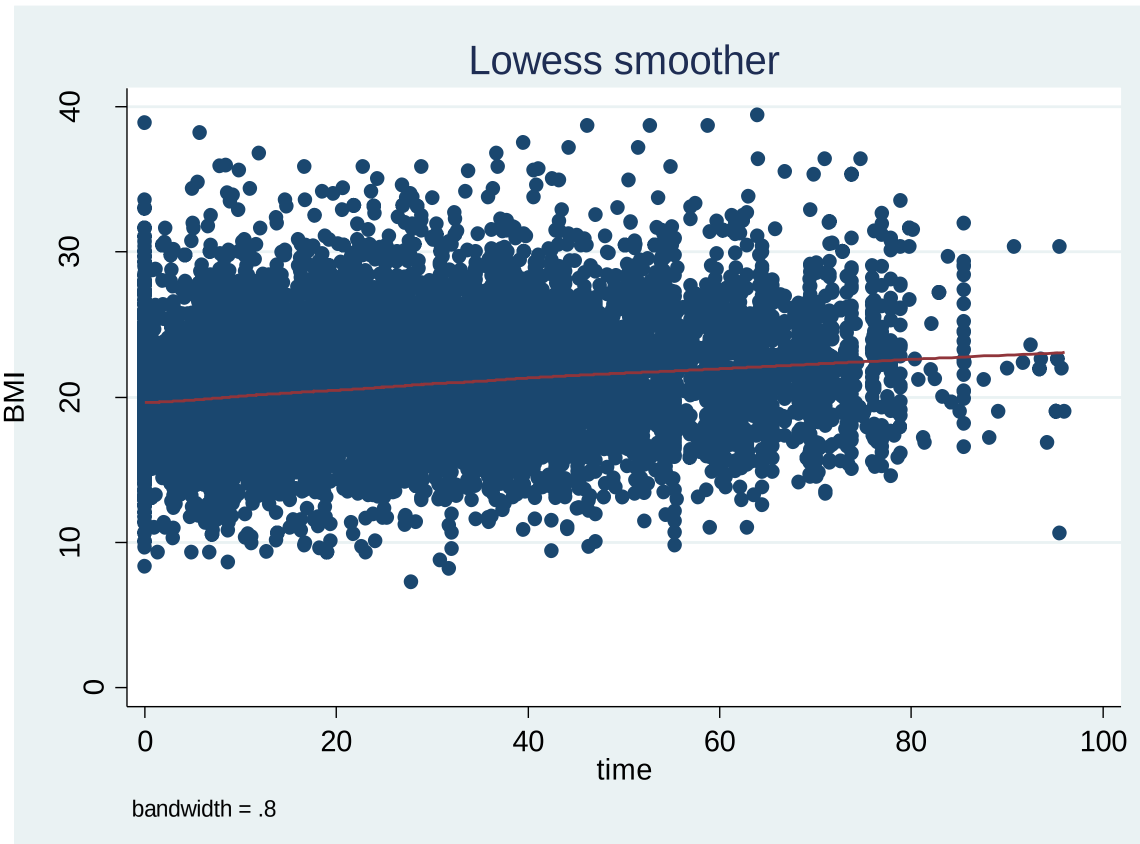


Figure 7Time plot of BMI versus time in months with lowess smoothed curve superimposed for HIV patients on second line ART in Amhara region 2008-2016

The mean profile of BMI shows a linear increase over time

5.4.4 Mean profile for females and males respectively

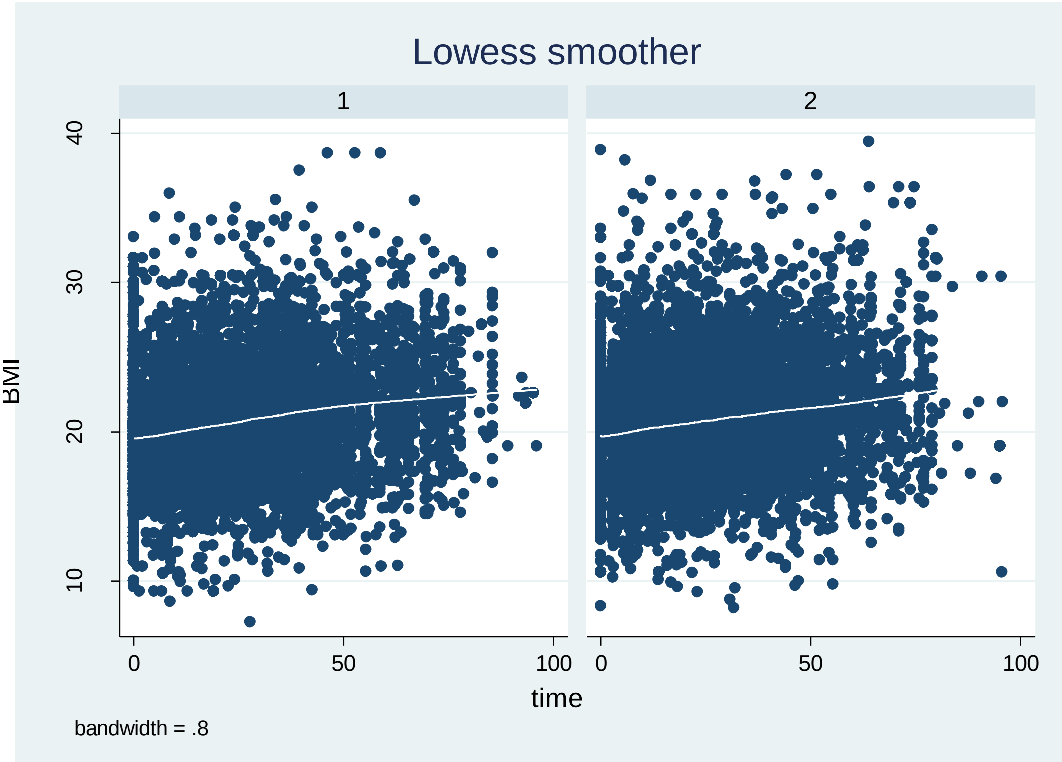


Figure 8 Time plot of BMI versus time in months with lowess smoothed curve superimposed for HIV patients on second line ART in Amhara region separated by sex 2008-2016

The plot shows a linear increment of BMI in both females (1) and males (2) over time.

5.5 Exploring the correlation structure and scatter plot of correlation matrix

Since this is a repeated measurement we expect some sort of correlation between consecutive measurements. In this case there is a positive correlation between subsequent measurements (table 3 , figure 10).

Table 3 Correlation matrix of BMI over time

	BMI0	BMI1	BMI2	BMI3	BMI4	BMI5	BMI6	BMI7	BMI8	BMI9	BMI10	BMI11	BMI12
BMI0	1.0000												
BMI1	0.8668	1.0000											
BMI2	0.7992	0.9248	1.0000										
BMI3	0.7902	0.8676	0.8963	1.0000									
BMI4	0.8416	0.9230	0.8988	0.9353	1.0000								
BMI5	0.8337	0.9164	0.9253	0.9155	0.9563	1.0000							
BMI6	0.4834	0.4246	0.3667	0.5032	0.4892	0.4901	1.0000						
BMI7	0.8655	0.8665	0.8470	0.8757	0.8972	0.9161	0.7251	1.0000					
BMI8	0.8666	0.9002	0.8961	0.9132	0.9333	0.9472	0.6097	0.9669	1.0000				
BMI9	0.8978	0.8795	0.8943	0.8725	0.9296	0.9356	0.5126	0.9258	0.9505	1.0000			
BMI10	0.8827	0.9198	0.9069	0.8907	0.9210	0.9282	0.5194	0.9352	0.9582	0.9568	1.0000		
BMI11	0.8619	0.8885	0.8830	0.8997	0.9194	0.9154	0.5677	0.9422	0.9618	0.9568	0.9722	1.0000	
BMI12	0.8359	0.8897	0.8822	0.8849	0.9138	0.9026	0.5704	0.9347	0.9508	0.9433	0.9743	0.9790	1.0000

Pair wise scatter plot matrix also showed a positive and linear relationship between BMI at different time points

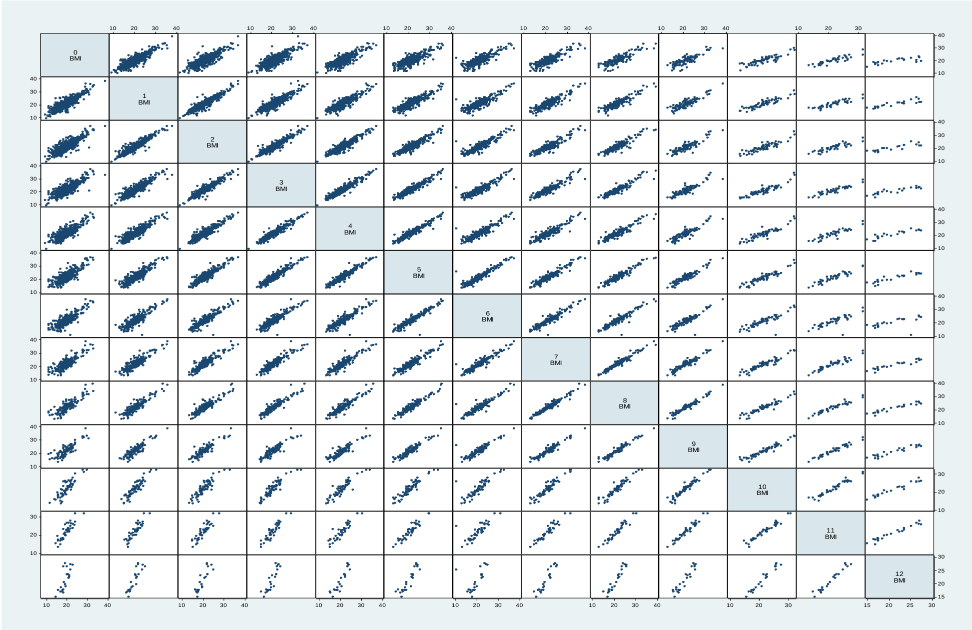


Figure 9 scatter plot matrix for pairs of observation times

The scatter plot matrix also shows a positive linear relationship between BMI measurements taken at subsequent measurements.

5.6 Univariate Marginal model

Predictor variables which show association at significance level of 0.25 were age, gender, CD4 count, WHO stage, functional status, educational status, occupational status, opportunistic infection, Tuberculosis, second line ART regimen, CPT, and INH.

Table 4 Correlation structure checking and model comparison

	Unstructured	Identity	Exchangeable
AIC	14337.93	17775.34	17666.17
BIC	14531.08	17956.02	17853.09

So the model with lowest AIC was chosen, in this case the unstructured correlation structure.
The need for random slop and intercept was checked by likelihood ratio test of model without a random intercept, with only random intercept and a model with both random intercept and slop.

Table 5 Random Effects Models comparison

Random effects	LR X^2	P value
Model1 intercept	5625.28	**0.0000**
Model2 intercept, time	297.13	**0.0000**

So as we can see from the above tables the inclusion of random intercept and random slop is reasonable so in the final model we have used both random intercept and random slop.

Normality assumption

The assumption of normality was checked by Q-Q plot. We have also compared the origional data with log and squre root transformed one (annex 1). Since approximately the origional one showed a lesser deviation from the normal line we have used the origional data for the final model

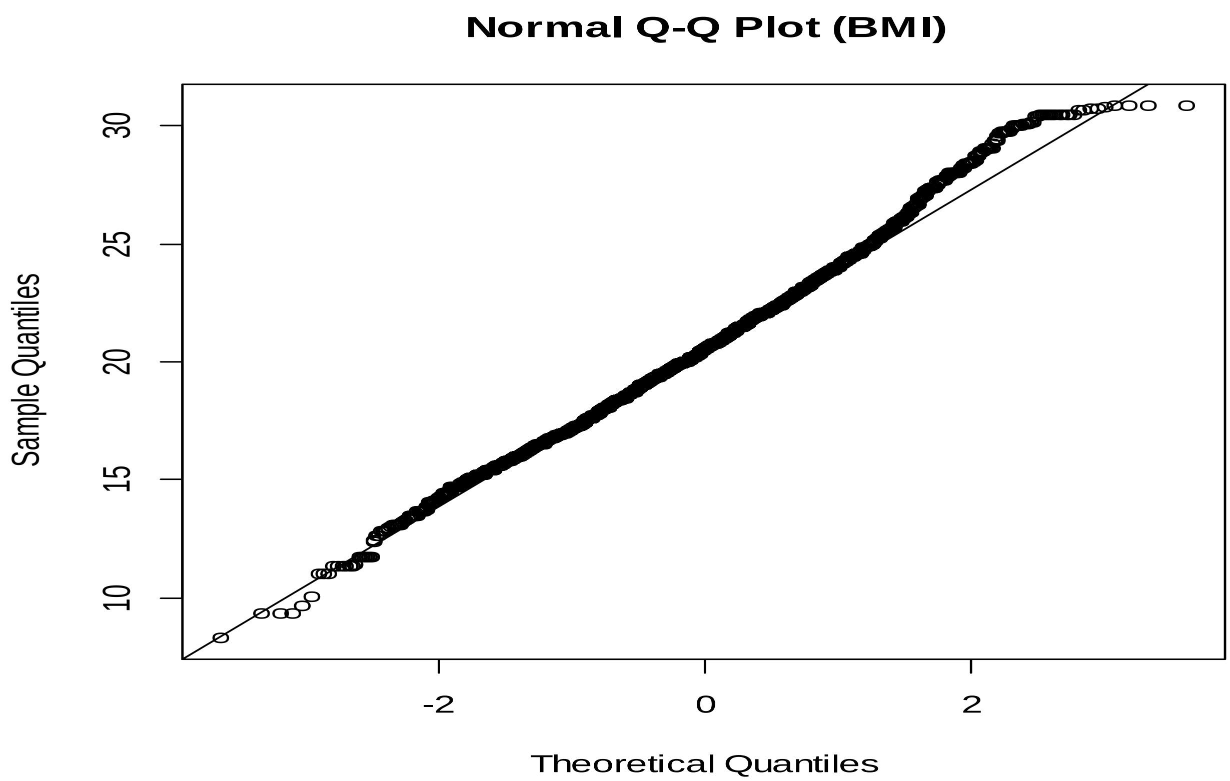


Figure 10 Normal Q-Q plot for BMI

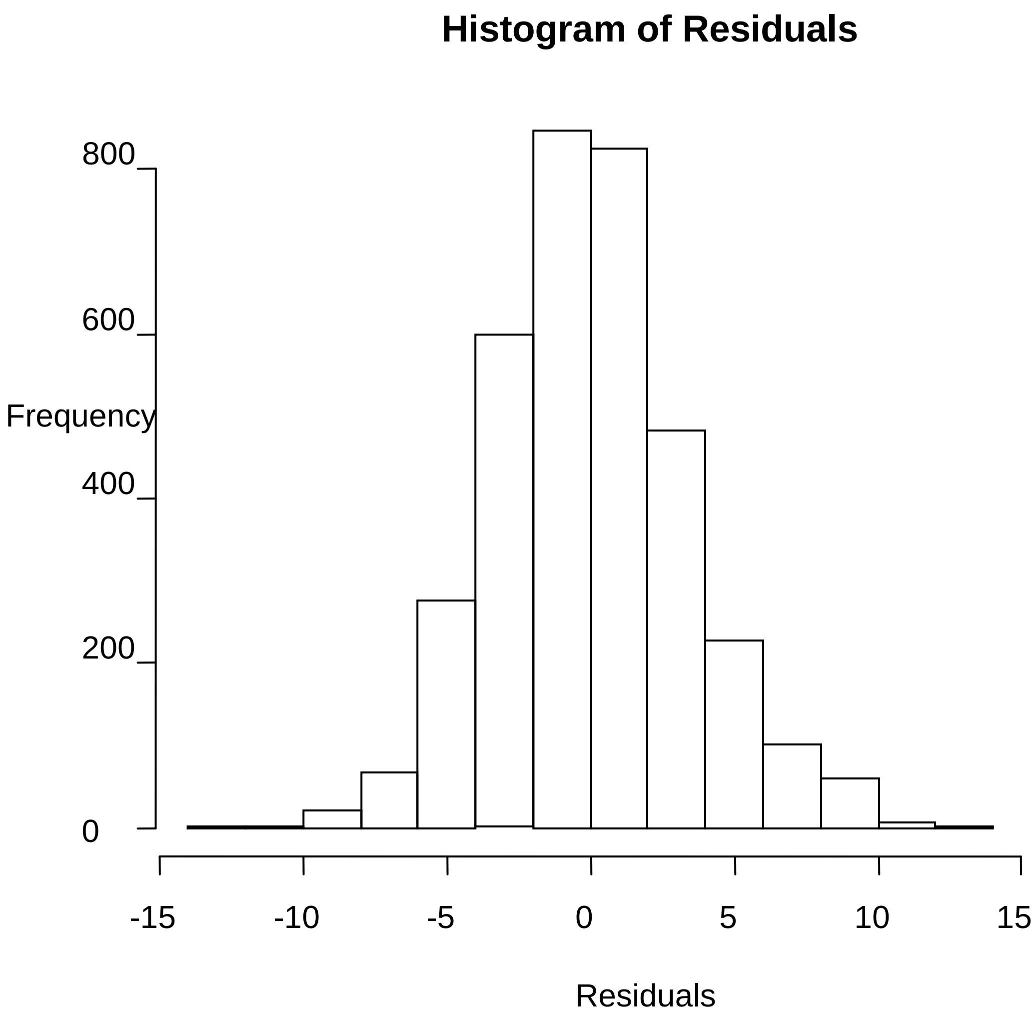


Figure 11 Histogram of residuals

The histogram of residuals show approximately normal distribution

5.7 Model diagnostics

We have checked the goodness of fit by making model diagnostic plot (Figure 8)

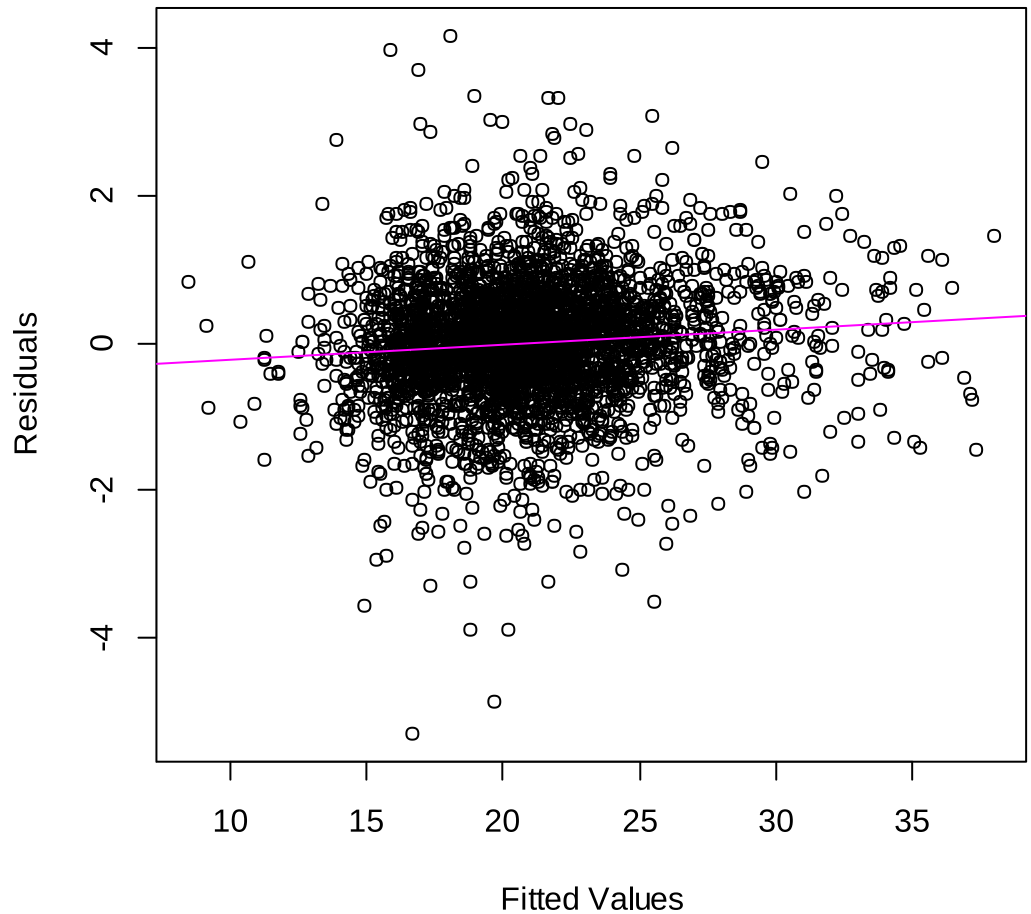


Figure 12 Model diagnostic plot

As we can see from the above plot the residuals are concentrated to the value of zero showing a good fit.

5.8 Factors affecting BMI

Factors found to have a significant effect on the evolution of BMI over time at multivariable linear mixed effect model were treatment duration, age, good adherence INH prophylaxis, CPT, NGO employement, ambulatory, bedridden, WHO stage III, WHO stage IV and CD4 count. Time interaction of tertiary education, ambulatory functional status, and WHO stage III had significant association.

The final model of this study is

BMI = 18.4 + 0.04(time) + 0.04(age) + 1.9 (Nongovemp.) + 0.6 (good adherence) + 0.7(INHgiven) + 0.8(CPTgiven) + 0.02(teritiaryedu#time) – 1.6(Ambulatory) + 0.3(Ambulatory#time) – 1.8(Bedridden) – 0.4 (WHOstageIII) + 0.01 (WHOstageIII#time) – 0.8 (WHOstageIV) + 0.001(CD4count)

As displayed above 3 continuous and 8 categorical variables, 3 predictors time interaction were significantly associated with BMI.

The intercept of BMI of patients was 18.4 kg/m^2 (95% CI 16.8, 20.05). When we see the variability explained by covariates considered keeping all other variables at constant, For a one month increase in treatment duration the BMI of patients increases by 0.04 (95% CI 0.01, 0.07). Patients who work in NGOs have a 1.9kg/m^2 (95% CI 0.24, 3.52) BMI increment when compared to governmental employees. But there were no significant difference between government employees and private, unemployed and others. For a unit increase in the age of a patient the BMI was increased by 0.04 (95% CI 0.01 0.07). When compared with patients with poor ART adherence those who had good adherence had increased BMI (β=0.6 95% CI 0.04, 1.14). Those individuals who took INH had a 0.7 kg/m^2 (95% CI 0.22, 1.36) increment in BMI as compared to their counter parts. Compared to patients who didn't take CPT those who took had their BMI increased by 0.8 kg/m^2 (95% CI 0.2, 1.3). Patients who attend tertiary school have better evolution in BMI when compared to those who lack formal education (β=0.02, 95% CI 0.003, 0.04). Individuals who were ambulatory and bedridden had decrement in their BMI by 1.6 kg/m^2 (95% CI -1.91, -1.26) and 1.8 kg/m^2 (95% CI -2.45, -1.21) respectively. And time interaction of ambulatory status showed a better evolution (β =0.03 95% CI 0.013, 0.05) as compared to those with working functional status.

Patients on WHO stage III and WHO stage IV have decreased BMI by 0.4 (95% CI -0.62, -0.16) and 0.8 (-1.17 -0.36) as compared to WHO stage I. And over time those at WHO stage III had a higher evolution (β=0.01 95% CI 0.01, 0.02) compared to WHO stage I. But no significant difference was seen between WHO stage I and WHO stage II. CD4 count of patients had also a positive association with BMI that is for a unit increase in CD4 count BMI increased by 0.001 kg/m^2 (95% CI 0.001, 0.001). The standard deviation of the intercept sd (constant) was 3.3 which shows a significant BMI difference between subjects at baseline and standard deviation of slop was 0.04 which shows that there is significant variation between individuals over time.

Table 6 Parameter estimates for full linear mixed effect model

BMI	Coefficient	[95% conf. interval]
INTERCEPT	18.4	(16.8, 20.05)***
Time	0.04	(0.01, 0.07)*
Sex(Female)	**0**	
Male	-0.16	(-0.67, 0.34)
Female#time	**0**	
Male#time	0.003	(-0.01, 0.01)
Age	0.04	(0.01 0 .07)**
Poor adherence	**0**	
Fair adherence	0.4	(-0.2, 1.06)
Good adherence	0.6	(0.04 1.14)*
Poor adherence#time	**0**	
Fair adherence#time	0.004	(-0.01, 0.18)
Good adherence#time	-0.002	(-0.01, 0.01)
INH given (No)	**0**	
INH given (Yes)	0.7	(0.22, 1.36)**
INH given(No)#time	**0**	
INH given(Yes)#time	0.004	(-0.01 , 0.01)
CPT given (No)	**0**	
CPT given (Yes)	0.8	(0.25, 1.39)**
CPT given (No)#time	**0**	
CPT given (Yes)	-0.015	(-0.02 , 0.03)
TB history (No)	**0**	
TB history (Yes)	-0.58	(-1.30, 0.14)
TB history (No)#time	**0**	
TB history (Yes)#time	-0.01	(-0.02 , 0.01)
OI (No)	**0**	
OI (Yes)	-0.53	(-1.12 , 0 .07)
OI(No)#time	**0**	
OI(Yes)#time	0.004	(-0.01 , 0 .02)
Occupation (Gov't)	**0**	

BMI	Coefficient	[95% conf. interval]
Unemployed	0.34	(-0.39 , 1.07)
NGO employee	1.9	(0.24, 3.52)*
Private	0.25	(-0.81 , 1.32)
Other	0.45	(-0.7 , 0.79)
Occupation(Gov't)#time	**0**	
Unemployed#time	0.05	(-0.01 , 0.02)
NGO employee#time	0.02	(-0.01 , 0.54)
Private#time	0.0002	(-0.21 , 0.22)
Others#time	0.005	(-0.01 , 0.02)
Education(Noeducation)	**0**	
Primary	-0.04	(-0.73 , 0 .66)
Secondary	0.56	(-0.12 , 1.25)
Tertiary	0.89	(-0.07 , 1.85)
No education#time	**0**	
Primary#time	-0.003	(-0.02 , 0.01)
Secondary#time	0.01	(-0.01 , .002)
Tertiary#time	0.02	(0.003 , 0.04)*
Functional (Working)	**0**	
Ambulatory	-1.6	(-1.91 -1.26)***
Bedridden	-1.8	(-2.45 -1.21)***
Functional (Worki)#time	**0**	
Ambulatory#time	0.03	(0.013 0.05)***
Bedridden#time	-0.004	(-0.04 0 .03)
WHO stage I	**0**	
WHO stage II	-0.01	(-0.39 0.38)
WHO stage III	-0.4	(-0.62 -0.16)***
WHO stage IV	-0.8	(-1.17 -0.36)***
WHO stage I#time	**0**	
WHO stage II#time	0.003	(-0.01 0.02)
WHO stage III#time	0.013	(0.01 0.02)***
WHO stage IV#time	-0.01	(-0.02 0 .012)

BMI	Coefficient	[95% conf. interval]
ART regimen (ABC based)	**0**	
TDF based regimen	0.3	(-0.27 0.85)
AZT based regimen	0.2	(-0.52 0.89)
Other regimens	-0.02	(-1.05 1.01)
ABC based regimen#time	**0**	
TDF based regimen#time	-0.01	(-0.02 0.002)
AZT based regimen#time	0.00001	(-0.02 0.02)
Other regimens#time	-0.02	(-0.03, .001)
CD4 count	0.001	(0.0007 0.0014)***

Random-effects Parameters	**Estimate**	**[95% Conf. Interval]**
id: Unstructured		
sd(time)	0.04	(0.036, 0.046)
sd(_cons)	3.3	(3.13, 3.48)
corr(time,_cons)	0.03	(-0.09, 0.14)
sd(Residual)	0.97	(0.94, 0.99)

LR test vs. linear model: chi2(3) = 5895.95 Prob > chi2 = 0.0000
*** P value < 0.001 ** P value < 0.01 *P value <0.05

6. DISCUSSION

This study has found a linear increment in BMI of patients over time. There were BMI differences between subjects at baseline and in their progress over time.
Factors related to increment in BMI were age, NGO employment, treatment duration, INH prophylaxis, CPT prophylaxis, CD4 count and good adherence. And factors associated with a negative change in BMI were ambulatory functional status, bedridden functional status, WHO stage III and WHO stage IV.

For a one month increase in treatment duration the BMI of patients increases by 0.04, this finding is in line with a study in South Africa (RRR = 1.01) (37). The possible reasons for weight gain could be due to normal reversion of the weight loss associated with HIV or due to drug related metabolic changes which include hyperlipidemia, insulin resistance and diabetes(38) Or due to the growing life style change of sub Saharan countries to European way of living which includes high energy intake, high dietary fat and sugar and less physical activity(39).

For a one unit increase in the age of a patient BMI was increased by 0.04 kg/m^2. The finding is in line with a study conducted in multicenter study in low resource setting which shows a lower probability of weight loss in older individuals when compared to younger age groups less than 29 years(13). A study conducted in Swiss also showed a similar but higher change in BMI with age (β = 0.15, 95% CI 0.06–0.24 kg/m^2) (40). This association could be due to increased risk of lipid accumulation in HIV patients as age increases(38)

Patients who work in NGOs have a 1.9kg/m^2 BMI increment when compared to governmental employees this could be due to a better payment in NGOs which helps them access a balanced diet and improve their health status(42).

There were no difference in BMI change in patients with different educational level at baseline but patients who have tertiary educational level have a higher evolution from those with no education (β=0.02). Possible reason can be a higher educational level enabling them to better understand and live a health conscious life style(43).

When compared with patients with poor ART adherence those who have good ART adherence had increased BMI by 0.6 kg/m^2. This finding is in line with a study in Hanoi, Vietnam, 2.6 kg increase in the first 6 months of treatment in those who have very good adherence(31) and in a study from South Africa also higher probability of weight gain was seen in those who have good adherence as compared to poor adherence, RRR 1.51.(37) The possible reason could be the strong association of good adherence to viral suppression and improved clinical outcome of therapy including weight gain(44).

Patients who took Isoniazid prophylaxis (INH) and Cotrimoxazole prophylaxis (CPT) have 0.8 and 0.7 kg/m^2 BMI increase when compared to their counter parts. This finding has similar association with a multicenter controlled clinical trial in Africa (45). This could be due to the greatly increased appetite associated with the prophylactic drugs(46). INH also augments the effect of ART (47).

Patients whose functional status was ambulatory and bedridden had a decreased BMI by 1.6 kg/m^2 and 1.8kg/m^2 respectively when compared to those who are working. This could be due to their inability to work they may not access nutritious and balanced diet which affects their BMI. Or it could be due to additional decreased immunity caused by physical inactivity which makes them more susceptible to minor infections leading to a higher calori loss (48) But those patients who were ambulatory have a higher evolution of BMI when compared to working (β=0.03, 95% CI 0.013, 0.05).

Patients on WHO stage III and WHO stage IV have decreased BMI by 0.4 and 0.8 respectively as compared to WHO stage I. and over time those at WHO stage III have a higher evolution (β =0.013 95% CI 0.01, 0.02). This finding is in line with a multicenter study in resource limited settings which shows individuals who had high clinical status (WHO stage III and WHO stage IV) had poorer weight gain when compared to weight change in patients at lower WHO stage -2.26 kg(13). The possible reason can be unexplained chronic diarrhea and HIV enteropathy in these patients and the associated malabsorption(7) or it could be due to pyrexia of unknown origin in the late stage of the disease which results an increased calori loss and wasting(49).

For a unit increase in CD4 count BMI was increased by 0.001 kg/m^2 this positive association is supported by evidence from a study conducted in Boston which states that for a unit increase in CD4 cells weight increases by 0.35 kg(14). A study from Tanzania also shows increment in weight with increment in CD4 count(30). This increase can be explained by association of increment of CD4 count with a good clinical changes like viral supression, improved immunity and apitite leading to increment in the BMI of patients (13).

Clinical and Public health importance of this study is health care professionals can monitor and follow the response of their patients on ART by easily available, inexpensive and good predictor of the outcome of therapy and know in which factors they can intervene.

Since viral load, CD4 count and other measurements are expensive and inaccessible, the ministry of health can consider BMI as initial predictor of treatment outcome in resource limited areas. It can help the public in general to access further investigations by early predicting the treatment success and easily intervene per findings.

Strength and limitation of the study

Being a retrospective study we were unable to find some predictors like viral load, alcohol and smoking marital status. The main strength of this study was the method of analysis, the use of longitudinal data analysis which can handle both time variant and non time variant covariates, good for missing data and irregularly spaced observations. This method also considers all sources of variation, time interaction effect of variables and subject specific parameters.

7. CONCLUSION

This study has found a linear increment in BMI of patients over time.
Factors related to increment in BMI are age, treatment duration, INH prophylaxis, CPT, NGO employment, CD4 count and good adherence.
Factors associated with a negative change in BMI were ambulatory functional status, bedridden functional status, WHO stage III and WHO stage IV.

8. RECOMMENDATION

To Health care providers

- ✓ We recommend the health professionals to provide INH and CPT prophylaxis to all patients giving a special attention for those who are on WHO stage III and IV.
- ✓ Health care providers shall give all possible interventions to improve adherence of patients and to make them stay long on treatment. They shall also consider the negative impacts of being overweight /obese.

To the government

- ✓ We suggest to give special support for patients who are bedridden and ambulatory.

To researcher

- ✓ Other important predictors like alcohol use, smoking, viral load need further study.
- ✓ The effect of increment in BMI of patients on cardiovascular disease needs further study.

9. REFERENCES

1. 20th International AIDS coference, Melbourne, Australia. Global Fact Sheet: HIV/AIDS. 2014.
2.UNSAID. Global AIDS update. 2016.
3.UNSAID. Begining of the end of the HIV epidemic THE GAP REPORT. 2014.
4.WHO. HIV/AIDS progress in 2014, Ethiopia | HIV/AIDS March 2015. available at http://wwwafrowhoint/en/ethiopia/country-programmes/topics/4480-hivaidshtml
5. Mahy M, Stover J, Stanecki K, Stoneburner R, Tassie J-M. Estimating the impact of antiretroviral therapy: regional and global estimates of life-years gained among adults. BMJ. 2017;available at http://sti.bmj.com/content/86/Suppl_2/ii67.full.pdf+html.
6. Health FMo. Health sector development program IV Annual performance report 2013/14 available at http://www.moh.gov.et/documents/26765/0/Annual+Perfomance+Report+2006+EFY/4f5a6b33-3ef1-4430-a0a0-21fa13221343?version=1.0.
7. Organization WH. Interim WHO Clinical Staging of HIV/AIDS AND HIV/AIDS Case Definitions for Surveillance, African Region. 2005.
8. Tang AM, Forrester J, Spiegelman D, Knox TA, Tchetgen E, Gorbach SL. Weight loss and survival in HIV-positive patients in the era of highly active antiretroviral therapy. Journal of acquired immune deficiency syndromes (1999). 2002 Oct 01;31(2):230-6. PubMed PMID: 12394802. Epub 2002/10/24. eng.
9. Wanke CA, Silva M, Knox TA, Forrester J, Speigelman D, Gorbach SL. Weight loss and wasting remain common complications in individuals infected with human immunodeficiency virus in the era of highly active antiretroviral therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2000 Sep;31(3):803-5. PubMed PMID: 11017833. Epub 2000/10/06. eng.
10. Koethe JR, Jenkins CA, Lau B, Shepherd BE, Silverberg MJ, Brown TT, et al. Body mass index and early CD4 T-cell recovery among adults initiating antiretroviral therapy in North America, 1998-2010. HIV medicine. 2015 Oct;16(9):572-7. PubMed PMID: 25960080. Pubmed Central PMCID: PMC4558259. Epub 2015/05/12. eng.
11. Sharma A, Hoover DR, Shi Q, Gustafson D, Plankey MW, Hershow RC, et al. Relationship between Body Mass Index and Mortality in HIV-Infected HAART Users in the Women's Interagency HIV Study. PloS one. 2015 12/23
04/14/received
11/09/accepted;10(12):e0143740. PubMed PMID: PMC4689347.
12. Kim DJ, Westfall AO, Chamot E, Willig AL, Mugavero MJ, Ritchie C, et al. Multimorbidity patterns in HIV-infected patients: the role of obesity in chronic disease clustering. Journal of acquired immune deficiency syndromes (1999). 2012 Dec 15;61(5):600-5. PubMed PMID: 23023101. Pubmed Central PMCID: PMC3508375. Epub 2012/10/02. eng.
13. Huisin 't Veld D, Balestre E, Buyze J, Menten J, Jaquet A, Cooper DA, et al. Determinants of Weight Evolution Among HIV-Positive Patients Initiating Antiretroviral Treatment in Low-Resource Settings. Journal of acquired immune deficiency syndromes (1999). 2015 Oct 01;70(2):146-54. PubMed PMID: 26375465. Pubmed Central PMCID: PMC4576726. Epub 2015/09/17. eng.

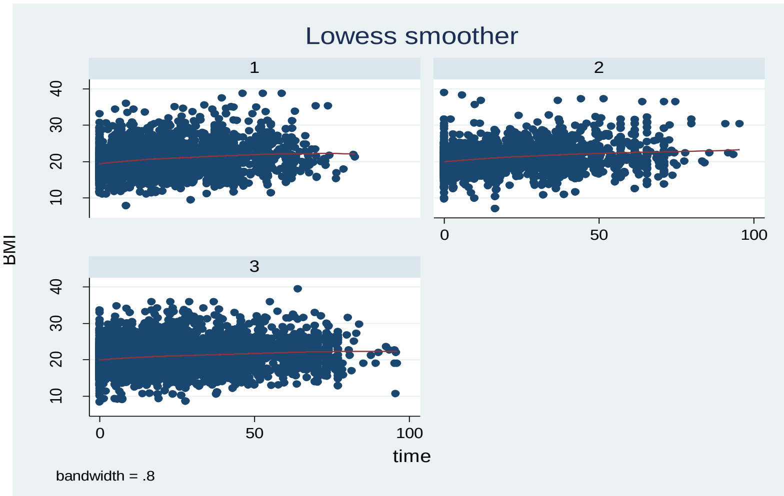
14. Mwamburi DM, Wilson IB, Jacobson DL, Spiegelman D, Gorbach SL, Knox TA, et al. Understanding the Role of HIV Load in Determining Weight Change in the Era of Highly Active Antiretroviral Therapy. Clinical Infectious Diseases. 2005;40(1):167-73.
15. Emmanuel EN, Patrice HM, NkomoAssoh, Sandrine D, Christiane KD, Guy N, et al. Predictive Factors of Clinical and Biological Evolution of HIV Patients under Antiretroviral Treatment in Douala- Cameroon. SciMedCentral. 08 July 2016 (2379-0636).
16. Chakravarty J, Sundar S, Chourasia A, Singh PN, Kurle S, Tripathy SP, et al. Outcome of patients on second line antiretroviral therapy under programmatic condition in India. BMC infectious diseases. 2015 Nov 14;15:517. PubMed PMID: 26572102. Pubmed Central PMCID: PMC4647630. Epub 2015/11/18. eng.
17. Achhra AC MA, Reiss P Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study. HIV medicine. 2015.
18. Tsegaye AT, Wubshet M, Awoke T, Addis Alene K. Predictors of treatment failure on second-line antiretroviral therapy among adults in northwest Ethiopia: a multicentre retrospective follow-up study. BMJ open. 2016 Dec 08;6(12):e012537. PubMed PMID: 27932339. Pubmed Central PMCID: PMC5168604. Epub 2016/12/10. eng.
19. Seyoum A, Ndlovu P, Zewotir T. Quasi-Poisson versus negative binomial regression models in identifying factors affecting initial CD4 cell count change due to antiretroviral therapy administered to HIV-positive adults in North-West Ethiopia (Amhara region). AIDS research and therapy. 2016;13:36. PubMed PMID: 27843481. Pubmed Central PMCID: PMC5103612. Epub 2016/11/16. eng.
20. Patel D, Desai M, Shah AN, Dikshit RK. Early outcome of second line antiretroviral therapy in treatment-experienced human immunodeficiency virus positive patients. Perspectives in clinical research. 2013 Oct;4(4):215-20. PubMed PMID: 24312889. Pubmed Central PMCID: PMC3835965. Epub 2013/12/07. eng.
21. Dalhatu I, Onotu D, Odafe S, Abiri O, Debem H, Agolory S, et al. Outcomes of Nigeria's HIV/AIDS Treatment Program for Patients Initiated on Antiretroviral Treatment between 2004-2012. PloS one. 2016;11(11):e0165528. PubMed PMID: 27829033. Pubmed Central PMCID: PMC5102414. Epub 2016/11/10. eng.
22. Asiimwe SB, Kanyesigye M, Bwana B, Okello S, Muyindike W. Predictors of dropout from care among HIV-infected patients initiating antiretroviral therapy at a public sector HIV treatment clinic in sub-Saharan Africa. BMC infectious diseases. 2016 Feb 01;16:43. PubMed PMID: 26832737. Pubmed Central PMCID: PMC4736127. Epub 2016/02/03. eng.
23. Thao VP, Quang VM, Wolbers M, Anh ND, Shikuma C, Farrar J, et al. Second-Line HIV Therapy Outcomes and Determinants of Mortality at the Largest HIV Referral Center in Southern Vietnam. Medicine. 2015 Oct;94(43):e1715. PubMed PMID: 26512561. Pubmed Central PMCID: PMC4985375. Epub 2015/10/30. eng.
24. Swain PK, Grover G. Determination of Predictors Associated With HIV/AIDS Patients on ART Using Accelerated Failure Time Model for Interval Censored Survival Data. 2016.
25. Rubaihayo J, Tumwesigye NM, Konde-Lule J, Makumbi F, Nakku EJ, Wamani H, et al. Trends and Predictors of Mortality Among HIV Positive Patients in the Era of Highly Active Antiretroviral Therapy in Uganda. Infectious disease reports. 2015 Aug

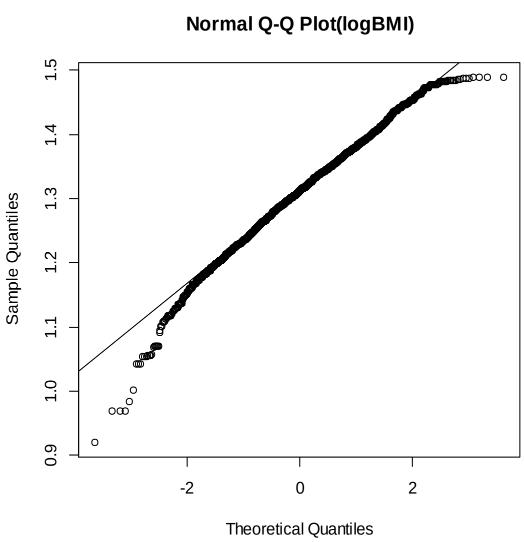
11;7(3):5967. PubMed PMID: 26500739. Pubmed Central PMCID: PMC4593885. Epub 2015/10/27. eng.
26. Damtew B, Mengistie B, Alemayehu T. Survival and determinants of mortality in adult HIV/Aids patients initiating antiretroviral therapy in Somali Region, Eastern Ethiopia. The Pan African medical journal. 2015;22:138. PubMed PMID: 26889319. Pubmed Central PMCID: PMC4742016. Epub 2016/02/19. eng.
27. Mave V, Erlandson KM, Gupte N, Balagopal A, Asmuth DM, Campbell TB, et al. Inflammation and Change in Body Weight With Antiretroviral Therapy Initiation in a Multinational Cohort of HIV-Infected Adults. The Journal of infectious diseases. 2016 Jul 01;214(1):65-72. PubMed PMID: 26962236. Pubmed Central PMCID: PMC4907416. Epub 2016/03/11. eng.
28. Guehi C, Badje A, Gabillard D, Ouattara E, Koule SO, Moh R, et al. High prevalence of being Overweight and Obese HIV-infected persons, before and after 24 months on early ART in the ANRS 12136 Temprano Trial. AIDS research and therapy. 2016;13:12. PubMed PMID: 26925155. Pubmed Central PMCID: PMC4768327. Epub 2016/03/01. eng.
29. Sicotte M, Langlois EV, Aho J, Ziegler D, Zunzunegui MV. Association between nutritional status and the immune response in HIV + patients under HAART: protocol for a systematic review. Systematic reviews. 2014 Feb 10;3:9. PubMed PMID: 24513015. Pubmed Central PMCID: PMC3922999. Epub 2014/02/12. eng.
30. Li N, Spiegelman D, Drain P, Mwiru RS, Mugusi F, Chalamilla G, et al. Predictors of weight loss after HAART initiation among HIV-infected adults in Tanzania. AIDS (London, England). 2012 Mar 13;26(5):577-85. PubMed PMID: 22156968. Epub 2011/12/14. eng.
31. Tang AM, Sheehan HB, Jordan MR, Duong DV, Terrin N, Dong K, et al. Predictors of Weight Change in Male HIV-Positive Injection Drug Users Initiating Antiretroviral Therapy in Hanoi, Vietnam. AIDS research and treatment. 2011;2011:890308. PubMed PMID: 21776380. Pubmed Central PMCID: PMC3137978. Epub 2011/07/22. eng.
32. Mashinya F, Alberts M, Colebunders R, Van Geertruyden JP. Weight status and associated factors among HIV infected people on antiretroviral therapy in rural Dikgale, Limpopo, South Africa. African journal of primary health care & family medicine. 2016 Nov 29;8(1):e1-e8. PubMed PMID: 28155318. Pubmed Central PMCID: PMC5153409. Epub 2017/02/06. eng.
33. KR D, SANJI N, AGGARWAL V, SR R, HS S, J K. CHANGES IN THE CD4 COUNTS, HEMOGLOBIN AND WEIGHT IN PATIENTS WITH HIV ALONE AND HIV-TB CO-INFECTION. ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH. 2014;2(0974-2441).
34. Mustapha K, Ehianeta T, Kirim R, Osungwu F, Oladepo D. Highly active antiretroviral therapy (HAART) and body mass index (BMI) relationship in people living with HIV/AIDS (PLWHA) in the Federal Capital Territory, Nigeria and the neighbouring states. Journal of AIDS and HIV Research. 2011;3(3):57-62.
35. Block JP, Subramanian SV, Christakis NA, O'Malley AJ. Population Trends and Variation in Body Mass Index from 1971 to 2008 in the Framingham Heart Study Offspring Cohort. PloS one. 2013 05/10
10/16/received 04/01/accepted;8(5):e63217. PubMed PMID: PMC3651246.

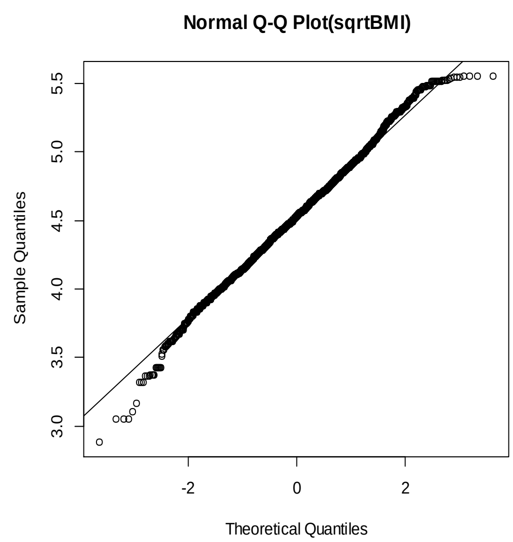
36. Muhammad F, Ramalan M, Enikuomehin A. Change in body mass index (BMI) after highly active antiretroviral therapy among hiv patients in Kano, Northwestern Nigeria. Endocrine Abstracts. 2017.
37. Huis In 't Veld D, Pengpid S, Colebunders R, Peltzer K. Body Mass Index and Waist Circumference in Patients with HIV in South Africa and Associated Socio-demographic, Health Related and Psychosocial Factors. AIDS and behavior. 2017 Feb 27. PubMed PMID: 28243935. Epub 2017/03/01. eng.
38. Montessori V, Press N, Harris M, Akagi L, Montaner JSG. Adverse effects of antiretroviral therapy for HIV infection. CMAJ : Canadian Medical Association Journal. 2004;170(2):229-38. PubMed PMID: PMC315530.
39. Micklesfield LK LE, Hume DJ. Socio-cultural, environmental and behavioural determinants of obesity in black South African women Cardiovasc J Afr. 2013.
40. Hasse B, Iff M, Ledergerber B, Calmy A, Schmid P, Hauser C, et al. Obesity Trends and Body Mass Index Changes After Starting Antiretroviral Treatment: The Swiss HIV Cohort Study. Open Forum Infectious Diseases. 2014 07/01 03/11/received 05/20/accepted;1(2):ofu040. PubMed PMID: PMC4281814.
41. Hinkin CH, Hardy DJ, Mason KI, Castellon SA, Durvasula RS, Lam MN, et al. Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. AIDS (London, England). 2004;18(Suppl 1):S19-S25. PubMed PMID: PMC2886736.
42. Makoba JW. Nongovernmental Organizations (NGOS) and Third World Development: An Alternative Approach to Development. Journal of Third World Studies Spring 2002.
43. Zimmerman EB, Woolf SH, Haley A. Understanding the Relationship Between Education and Health. Agency for healthcare research and quality. 2014.
44. Elul B, Basinga P, Nuwagaba-Biribonwoha H, Saito S, Horowitz D, Nash D, et al. High Levels of Adherence and Viral Suppression in a Nationally Representative Sample of HIV-Infected Adults on Antiretroviral Therapy for 6, 12 and 18 Months in Rwanda. PloS one. 2013 01/09 08/07/received 11/30/accepted;8(1):e53586. PubMed PMID: PMC3541229.
45. Haller L, Sossouhounto R, Coulibaly IM, Dosso M, Kone M, Adom H, et al. Isoniazid plus sulphadoxine-pyrimethamine can reduce morbidity of HIV-positive patients treated for tuberculosis in Africa: a controlled clinical trial. Chemotherapy. 1999 Nov-Dec;45(6):452-65. PubMed PMID: 10567776. Epub 1999/11/24. eng.
46. I. S. MUDIE, D.T.M.&H.N. W. HORNE, J. W. CROFTON, Isoniazide and weight gain BRIIIsH MEDICAL JOURNAL, 1954
47. WHO. HIV/AIDS 2014 available at http://www.who.int/hiv/topics/tb/3is_ipt/en/
48. Nieman, D. C. Exercise, infection, and immunity International journal of sports medicine 1994 PubMed PMID 7883395.
49. Hot, A, Schmulewitz, L, Viard, J. P, Lortholary, O. Fever of unknown origin in HIV/AIDS patients, Infect Dis Clin North Am. 2007; 21(4) PubMed PMID: 18061087.

10. ANNEX

Normal Q-Q plot and mean profile by adherence level







Data collection Check list

This checklist is prepared for the collection of socio-demographic, clinical, immunological, treatment and outcome related information that are important for the assessment of weight of HIV patients on second line ART in University of Gondar Hospital, FelegeHiwot referral Hospital, Debremarkos, Debrebirhan, Dessee referral hospital Woldya hospital,Debre Tabor Hospital and Finoteselam hospital. All this information will be retrieved from the clients ART registration book and from individual patient card without mentioning the name of clients. This information will be collected by health care providers (BSc nurse or Health Officer) possibly working in the ART clinic of the hospitals. Contact +251918068580

Part I: Baseline variables

S.No	**Variables**	**Categories**					
101.	Hospital/Facility						
102.	Patient_MRN number						
103.	Patient-ART number						
104.	Age at enrollment						
105.	Date of enrollment	----/-----/-----					
106.	Gender	1 Female	2 Male				
107.	Address	Zone__________	Woreda______		Kebele________		
108.	Marital status	1. Single	2. Married	3.Divorced	4. Widowed	5. Separated	
109.	Education	1.No education	2.Elementary	3 .Secondary	4 .Tertiary		
110.	Occupation	1.Unemployed	2.Government	3.Non gov't	4. Private	5 .Other	
111.	Pastopportunistic infections	1 Yes	2. No	112a. If yes,	Specify _____		
112.	Past TB treatment history	1. Yes	2. No	3. Not recorded			
113.	Is the treatment completed?	1. Yes	2. No				
114.	Substance use	1 Tobacco	2. Alcohol	3. Khat	4. None		
115.	Baseline Weight	____________kg					
116.	Baseline Height	____________m					
117.	Base line CD4	-------					
118.	Baseline WHO stage	1 Stage I	2. Stage II	3. Stage III	4. Stage IV		
119.	Baseline Functional status	1 Working	2.Ambulatory	3. Bedridden			
120.	Date the regimen changed to second line	-----/-----/-------- (DD/MM/YY)					
121.	Second line regimen	1. 2a 2. 2b	3. 2c 4. 2d	5. 2e 6. 2f	7. 2g 8. 2h	9. 2i 10. Other----	
122.	Viral load at switch	1. Undetectable(<400 cell/ml)		2. 400-10,000c/ml		3.>10,000c/ml	3. Not done

Part III: Follow-up variables after switch to second line ART

Date ofsecond lin Followup	Weight	Functional Status	WHO stage	TB screen (P/N)	OIs	INH	CPT	ARV drug							
								Adherence	**Code of** …	Regimen change(Y/N)	R. for change	Side effect	Hemoglobin level	CD4 count	BMI

Collected by: Name _____________________________ Signature _____________ Date _________________

Supervised by: Name ____________________________ Signature _____________ Date ________________

Declaration

I, the under signed, senior MPH student declare that this thesis report is my original work in partial fulfillment of the requirement for the degree of Master of Public Health in Epidemiology and Biostatistics.

Name: Adhanom G/Egziabher

Signature: _______________

Place of submission: Institute of public Health, College of Medicine and Health Sciences, University of Gondar.

Date of Submission: _________________

This thesis report has been submitted for evaluation with our approval as university advisors.

Advisors

Name	Signature
1. Mr.Lemma Deresh	-------------------------------
2. Mr.Ejigu Gebeye	-------------------------------